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**EP-A-0 062 391
NL-A-6 515 174**

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Description

This invention concerns a pharmaceutical pellet of the kind (hereinafter termed 'of the kind referred to') intended to be administered to a ruminant to reside in its rumeno-reticular sac and release predetermined quantities of one or more biologically-active substances over an extended period of time.

One known form of pellet of the kind referred to containing an active substance in the form of an anthelmintic material comprises a casing in the form of a metal tube having, as end caps, porous membranes through which the anthelmintic is discharged over an extended period of time. Disadvantages of such a pellet include its bulk, the fact that the casing may be retained within the rumen after the active substance has been fully dissipated and, most importantly, that the continuous discharge of the active substance at a low rate over an extended period tends to engender immunity in the parasites against which it is intended to be effective.

A second known form of pellet, as disclosed in EP.A—0 062 391 (Research Corporation), also comprises a body which is impermeable and resistant to attack by rumen juices but has at least one open end. In this case, however, the body is provided with a plurality of internal cellulosic partitions which are spaced apart to define a series of compartments or cavities, each containing a dosage of a biologically active substance. Such a pellet has similar disadvantages to the other prior art pellet since in practice, the active substance is discharged substantially continuously due to dissolution or diffusion through the cellulosic partitions.

An object of the present invention is to provide an improved pharmaceutical pellet of the kind referred to which overcomes these disadvantages and provides the pulsed release of an active substance at relatively infrequent intervals.

With this object in view, the present invention provides a pharmaceutical pellet of the kind referred to comprising an assembly of a plurality of plates axially spaced to define cavities therebetween, a biologically active substance in each said cavity and a retaining water impermeable sleeve or sheath protecting the assembly from attack by rumen juices except at one axial end or both axial ends thereof, characterised in that the plates are formed of a magnesium alloy so that, in use, the pellet releases sequential and alternate doses of magnesium and the biologically active substance.

Preferably a weighting slug is incorporated at one axial end to ensure that the pellet will remain in the rumenoreticular sac until all of the active substance has been consumed. This weighting slug is preferably enclosed by the sleeve.

The invention will be described further, by way of example, with reference to the accompanying drawing, in which:

Fig. 1 is a sectional elevation illustrating a first embodiment of the pellet of the invention, the section being taken longitudinally of the pellet;

Fig. 2 is a view comparable with Fig. 1, but illustrating a second embodiment of the pellet of the invention;

Fig. 3 is a view comparable with Figures 1 and 2, but showing a third embodiment; and

Fig. 4 is a similar view showing yet a further embodiment.

Referring firstly to Figure 1, a first embodiment of the pharmaceutical pellet conforming to the present invention comprises an assembly, indicated generally by the reference numeral 10, consisting of a plurality of circular plates or discs 12, of a magnesium alloy (whose composition will be discussed in greater detail hereinafter) each formed with a first axially-extending circular peripheral skirt (or flange) 14 on one of its faces and a second axially-extending circular skirt 16 on the other of its faces, the second skirt 16 being inwardly spaced from the periphery of the plate 12. As can be seen the assembly 10 comprises a plurality of the plates 12 interengaged with one another by each skirt 16 engaging into the skirt or flange 14 of the next adjacent plate 12, each skirt 16 defining a respective cavity 18 between its plate 12 and the next adjacent plate 12. Preferably the skirts 14 and 16 interengage with a tight interference fit to give mechanical strength to the assembly 10.

A relatively dense or heavy weighting slug 20 completes the assembly 10, being in the form of an end cap having a flange 22 which fits onto the exposed endmost skirt 16. This slug 20 forms a closure of the cavity 18 defined by the skirt 16 of the corresponding endmost plate 12.

Each of the cavities 18 contains a dose or filling 24 of a biologically-active substance, such as an anthelmintic material which may be in tablet, powdered, paste or other practical form.

A sheath 26 of water-impermeable plastics or similar material covers the entire outer surface of the assembly 10 save for the end thereof remote from the slug 20, which end is exposed.

In use the pellet is introduced into the rumenoreticular sac of an animal to be treated by use of an oesophageal balling gun. Whilst the pellet remains in the sac, the rumen juices dissolve the successive plates 12, in turn from the end remote from the slug 20, over a period of time, typically several weeks or even months, thus to release the successive doses 24 of the biologically-active material at timed intervals. The time taken for each plate 12 to dissolve is determined by its thickness and composition. After the last plate 12 has been dissolved, the rumen juices will eventually dissolve the slug 20, and the residual sheath 26 then becomes free to be discharged by excretion or vomiting.

Typically, for cattle, each pellet might have an overall length of 55 mm, a diameter of 28 mm and deliver seven 700 mg doses 24 over a period of six months, although the embodiment shown in Figure 1 is, of course, adapted only to deliver

six doses and fewer than six plates 12 or more than seven such plates 12 may be embodied in different embodiments as may be desired.

The sheath 26 may be formed by dipping the assembled discs 12 (with their doses 24) and the slug 20 into a suitable resin coating. As an alternative, it may be formed by shrinking a sleeve of thermo plastics material, such as poly-vinyl-chloride, thereon, or by assembling the components successively into a preformed sleeve.

Referring now to Figure 2, the pellet here shown is generally similar to that above described. However, in this example, assembly 30 comprises plates 32 in the form of discs which do not have outwardly projecting skirts and are spaced apart by doses 34 of biologically-active material in the form of compressed tablets, one such tablet 34 being provided between one endmost plate 32 and an adjacent weighting slug in the form of a plain end plug 36. The assembly 30 is enclosed by a sheath or sleeve 38 similar to that of the embodiment of Figure 1 as above described.

Figure 3 of the drawings illustrates a third embodiment of the pellet of the invention. This pellet is very similar to that of Figure 2 and accordingly similar reference numerals have been allocated to those parts which are similar to those already described. It differs from that of Figure 2, however, in that it does not incorporate a weighting slug and in that it has both axial ends exposed so that the doses 34 and plates 32 are dissolved from both ends of the pellet. These two features, namely the omission of the weighting slug and the exposure of the two ends of the pellet can, of course, be applied either singly or in combination to the embodiments of Figures 1 and 2.

The embodiment of Fig. 4 is similar to that of Figure 3, and again similar reference numerals have been allocated to similar parts. This embodiment differs from that of Figure 3 in that it incorporates a weighting slug 36 approximately midway along its length.

In order to be sure that, in practical use, the pellet of the invention will remain in the rumen-reticular sac, it is appropriate that it should have a minimum density of about 2.25 g/ml and of course its density will usually increase as it dissolves since the active material will, normally, be less dense than the alloy of the plates 12, 32 and the metal of the slug 20, 36, when provided, and the proportion of metal to active material increases with consumption of the pellet.

The magnesium alloy of which the plates 12, 32 are made may contain from 0 to 15% of Aluminium, from 0 to 6% Copper, from 0 to 5% Zinc, from 0 to 2% Nickel and from 0 to 0.5% Cobalt, these percentages being by weight. A preferred alloy comprises 12% Aluminium, 2% Copper and 86% Magnesium.

The slug 20, 36 is preferably a Zinc-based alloy containing from 5% to 25 by weight Magnesium, which aids its eventual degradation by the rumen juices, but it may be of iron or other suitable

material which will be gradually dissolved or consumed.

It will be appreciated that it is not intended to limit the invention to the above examples only, many variations, such as might readily occur to those skilled in the art, being possible, without departing from the scope of the claims appearing at the conclusion hereof.

For example, the doses 24, 34 may be provided by substances other than anthelmintics, or they may comprise other active agents in conjunction with anthelmintics.

In each of the embodiments of Figures 1 and 2, an additional dose (not shown) of active substance may be incorporated at the exposed end, not enclosed by the sheath or sleeve 26, 38, of the assembly 10, 30 whereby a first dose is delivered immediately upon administration of the pellet. In the embodiment of Figure 3, the arrangement may be such that an active substance dose 34 is initially exposed at each end, or such that there is an active substance dose 34 exposed at one end and a plate 32 exposed at the other end.

Active agents incorporated in the pellets of the invention may include anti-bacterials, anti-coccidials, anti-protozoals, anti-theilerials, anti-fungals, anti-virals, insecticides, acaricides, growth promoters, nutrients, anti-biotics and trace elements such as copper, cobalt, selenium and their compounds. These agents may, of course, be included separately or in combination. The preferred anthelmintic is oxfendazole, lasalocid (Trade Mark) or the compound known as M-139603 described in detail in United Kingdom Patent Specification No. 2027013B being preferred anti-coccidials. Another preferred anthelmintic is levamisole.

Claims

1. A pharmaceutical pellet (10, 30) of the kind intended to be administered to a ruminant to reside in its rumen-reticular sac and release predetermined quantities of biologically active substances over an extended period of time, said pellet comprising an assembly of a plurality of plates (12, 32) axially spaced to define cavities (18) therebetween, a biologically active substance in each said cavity and a retaining water impermeable sleeve or sheath (26, 38) protecting the assembly (10, 30) from attack by rumen juices except at one axial end or both axial ends thereof, characterised in that the plates are formed of a magnesium alloy so that, in use, the pellet releases sequential and alternate doses of magnesium and the biologically active substance.

2. A pharmaceutical pellet according to claim 1 further characterised in that a weighting slug (20, 36) is incorporated approximately at the middle or at one axial end of the assembly.

3. A pharmaceutical pellet according to claim 2 wherein the weighting slug (20, 36) is at one end and is enclosed by the sleeve.

4. A pharmaceutical pellet according to claim 1, 2 or 3 wherein each plate is in the form of a disc

(32), the biologically-active substance being present as tablets (34) one of which is present between each adjacent pair of said discs (32).

5. A pharmaceutical pellet according to claims 2 and 4, or in claims 3 and 4, wherein a further said tablet is provided between the weighting slug (20, 36) and the endmost disc thereadjacent.

6. A pharmaceutical pellet according to claim 1, 2 or 3 wherein each plate has on one face a first peripheral skirt or flange (14) and on its other face a second skirt (16) inwardly-spaced from its periphery, the second (16) and first (14) skirts respectively of adjacent said discs (12) locating the one within the other to define respective cavities (18) each of which accommodates a respective dose or filling of said active substance.

7. A pharmaceutical pellet according to claim 6 wherein said second and first skirts (16, 14) are a tight interference fit the one within the other.

8. A pharmaceutical pellet according to any preceding claim wherein the sleeve (26, 38) or sheath is of a plastics material.

9. A pharmaceutical pellet according to any preceding claim and of which only one axial end is exposed, said exposed end containing a dose of the active agent exposed for immediate delivery upon administration of the pellet.

10. A pharmaceutical pellet according to any preceding claim wherein the magnesium alloy of the plates contains 0 to 15% Aluminium, from 0 to 6% Copper, from 0 to 5% Zinc, from 0 to 25% Nickel and from 0 to 0.5% Cobalt, the percentages being by weight.

11. A pharmaceutical pellet according to claim 2 or 3 wherein the weighted slug is of iron or of a Zinc-based alloy.

12. A pharmaceutical pellet according to any preceding claim wherein the active agent is selected from oxfendazole, lasalocid (Trade Mark), M—139603, and levamisole.

Patentansprüche

1. Pharmazeutisches Pellet (10, 30), das zur Verabreichung an einen Wiederkäuer vorgesehen ist und in dessen Pansen-Blindsack liegen und vorbestimmte Mengen von biologisch aktiven Substanzen über einen längeren Zeitraum abgeben soll, wobei das Pellet einen Aufbau aus mehreren Platten (12, 32), die axial mit einem Zwischenraum angeordnet sind, um Hohlräume (18) dazwischen zu bilden, eine biologisch aktive Substanz in jedem Hohlräum und eine wasserzurückhaltende, undurchlässige Buchse oder Hülse (26, 38) enthält, die den Aufbau (10, 30) gegen Angriffe durch Pansensaft, ausgenommen an einem axialen Ende oder an beiden axialen Enden schützt, dadurch gekennzeichnet, daß die Platten aus einer Magnesiumlegierung so ausgebildet sind, daß das Pellet bei Verwendung regelmäßig und abwechselnd Dosen von Magnesium und der biologisch aktiven Substanz freisetzt.

2. Pharmazeutisches Pellet nach Anspruch 1, weiterhin gekennzeichnet dadurch, daß ein beschwerender Block (20, 36) etwa in der Mitte

oder an einem axialen Ende des Aufbaus eingebaut ist.

3. Pharmazeutisches Pellet nach Anspruch 2, worin sich der beschwerende Block (20, 36) an einem Ende befindet und von der Buchse eingeschlossen ist.

4. Pharmazeutisches Pellet nach Anspruch 1, 2 oder 3, worin jede Platte Scheibenform (32) aufweist, die biologisch aktive Substanz in Form von Tabletten (34) vorliegt, wovon eine zwischen jedem benachbartem Paar von Scheiben (32) vorhanden ist.

5. Pharmazeutisches Pellet nach Anspruch 2 und 4 oder 3 und 4, worin eine weitere Tablette zwischen dem beschwerenden Block (20, 36) und der letzten benachbarten Scheibe vorgesehen ist.

6. Pharmazeutisches Pellet nach Anspruch 1, 2 oder 3, worin jede Platte auf einer Oberfläche eine erste periphere Einfassung oder einen Flansch (14) und auf der anderen Oberfläche eine zweite Einfassung (16), die von außen nach innen mit Abstand zum Rand davon vorhanden ist, aufweist, und wobei die zweite (16) bzw. die erste (14) Einfassung von jeweils benachbarten Scheiben ineinander fixiert sind, um einen entsprechenden Hohlräume zu bilden, wobei in jedem Hohlräum eine entsprechende Dosis oder Füllung des Wirkstoffs Platz hat.

7. Pharmazeutisches Pellet nach Anspruch 6, worin die zweite und die erste Einfassung (16, 14) ineinander dicht gepreßt sitzen.

8. Pharmazeutisches Pellet nach einem der vorhergehenden Ansprüche, worin die Buchse (26, 38) oder Hülse aus einem Plastikmaterial besteht.

9. Pharmazeutisches Pellet nach einem der vorhergehenden Ansprüche und bei dem nur ein axiales Ende offen ist, wobei das offene Ende eine Dosis des aktiven Mittels enthält, das für eine sofortige Freisetzung bei Verabreichung des Pellets frei liegt.

10. Pharmazeutisches Pellet nach einem der vorhergehenden Ansprüche, worin die Magnesiumlegierung der Platten 0 bis 15% Aluminium, 0 bis 6% Kupfer, 0 bis 5% Zink, 0 bis 25% Nickel und 0 bis 0,5% Kobalt, in Gewichtsprozent, enthält.

11. Pharmazeutisches Pellet nach Anspruch 2 oder 3, worin der beschwerende Block aus Eisen oder einer Legierung auf Zinkbasis ist.

12. Pharmazeutisches Pellet nach einem der vorhergehenden Ansprüche, worin das aktive Mittel aus Oxfendazol, Lasalocid (Warenzeichen), M—139603 und Levamisol ausgewählt ist.

Revendications

1. Comprimé pharmaceutique (10, 30) du genre prévu pour être administré à un ruminant afin qu'il séjourne dans le sac ruménoréticulaire et libère des quantités déterminées au préalable de substances biologiquement actives au cours d'une longue durée, lequel comprimé comprend un assemblage de plusieurs plaques (12, 32) axialement espacées pour définir des cavités (18)

entre elles, une substance biologiquement active dans chacune de ces cavités et un manchon ou gaine de retenue imperméable à l'eau (26, 38) protégeant l'assemblage (10, 30) contre l'attaque par les sucs du rumen, sauf à une de ses extrémités axiales ou aux deux, caractérisé en ce que les plaques sont formées d'un alliage de magnésium de façon qu'à l'usage le comprimé libère des doses successives et alternées de magnésium et de la substance biologiquement active.

2. Comprimé pharmaceutique suivant la revendication 1, caractérisé, en outre, en ce qu'une masse de lestage (20, 36) est incorporée à peu près au milieu ou à une extrémité axiale de l'assemblage.

3. Comprimé pharmaceutique suivant la revendication 2, dans lequel la masse de lestage (20, 36) se trouve à une extrémité et est enveloppée par le manchon.

4. Comprimé pharmaceutique suivant la revendication 1, 2 ou 3, dans lequel chaque plaque a la forme d'un disque (32), la substance biologiquement active étant présente sous forme de pastilles (34) dont une est présente entre chaque paire adjacente de ces disques (32).

5. Comprimé pharmaceutique suivant les revendications 2 et 4, ou suivant les revendications 3 et 4, dans lequel une telle pastille supplémentaire est disposée entre la masse de lestage (20, 36) et le disque d'extrémité qui lui est adjacent.

6. Comprimé pharmaceutique suivant la revendication 1, 2 ou 3, dans lequel chaque plaque comprend sur une face une première jupe ou couronne périphérique (14) et sur son autre face une seconde jupe (16) écartée vers l'intérieur de

sa périphérie, la seconde jupe (16) et la première (14) respectivement, de disques adjacents (12) s'emboîtant l'une dans l'autre pour définir des cavités respectives (18) dont chacune contient une dose ou charge respective de la substance active.

5 7. Comprimé pharmaceutique suivant la revendication 6, dans lequel les seconde et première jupes (16, 14) sont emboîtées avec serrage l'une dans l'autre.

10 8. Comprimé pharmaceutique suivant l'une quelconque des revendications précédentes, dans lequel le manchon (26, 38) ou gaine est fait d'une matière plastique.

15 9. Comprimé pharmaceutique suivant l'une quelconque des revendications précédentes, dont une seule extrémité axiale est exposée, cette extrémité exposée contenant une dose de l'agent actif exposée en vue du dégagement immédiat 20 lors de l'administration du comprimé.

10 10. Comprimé pharmaceutique suivant l'une quelconque des revendications précédentes, dans lequel l'alliage de magnésium des plaques contient 0 à 15% d'aluminium, 0 à 6% de cuivre, 0 25 à 5% de zinc, 0 à 25% de nickel et 0 à 0,5% de cobalt, le pourcentage étant sur base pondérale.

25 11. Comprimé pharmaceutique suivant la revendication 2 ou 3, dans lequel la masse de lestage est faite de fer ou d'un alliage à base de zinc.

30 12. Comprimé pharmaceutique suivant l'une quelconque des revendications précédentes, dans lequel l'agent actif est choisi entre l'oxfendazole, le Lasalocid (marque de produit), le M—139603 et le lévamisole.

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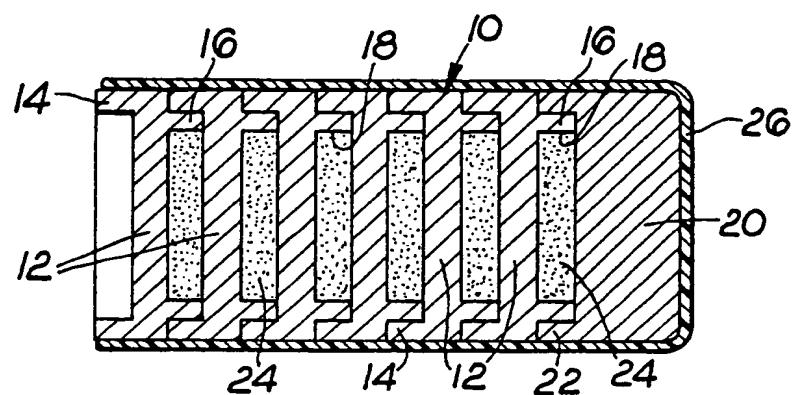


Fig. 1

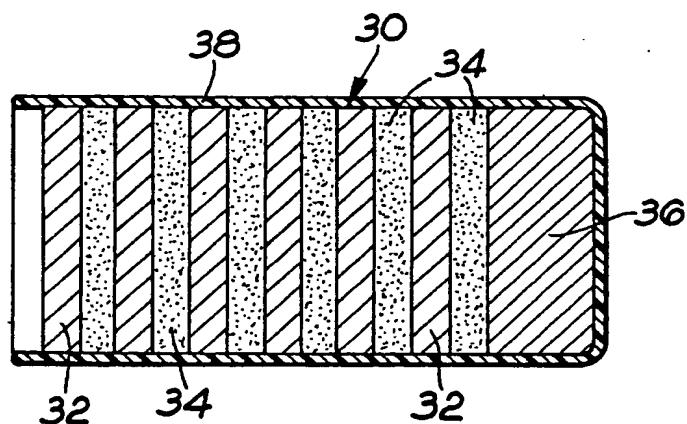


Fig. 2

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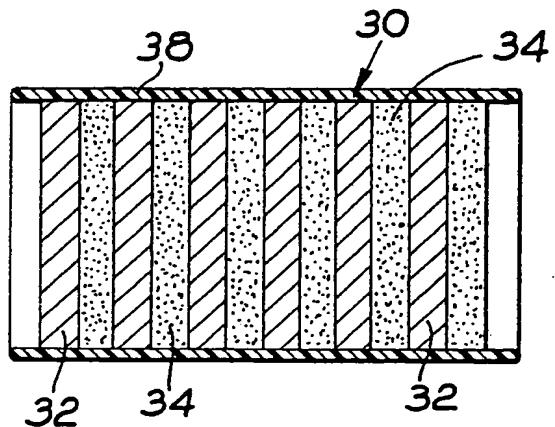


Fig. 3

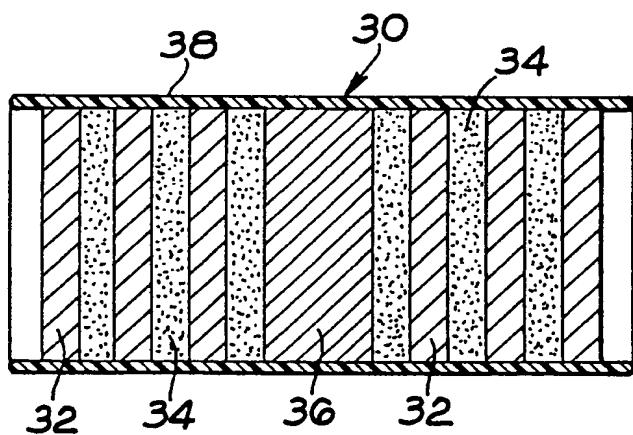


Fig. 4